M.H

ATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 December 1999 (06.12.99)	
International application No. PCT/US99/08371	**Applicant's or agent's file reference** 23201001/PCT
International filing date (day/month/year) 16 April 1999 (16.04.99)	**Priority date** (day/month/year) 16 April 1998 (16.04.98)
Applicant KORENBERG, Julie, R. et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   16 November 1999 (16.11.99)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Diana Nissen

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREA

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
KLAUBER & JACKSON
Attn. JACKSON, D.
411 Hackensack Avenue
Hackensack, New Jersey 07601
UNITED STATES OF AMERICA

RECEIVED
MAR 20 2000
KLAUBER & JACKSON

Date of mailing *(day/month/year)* 07/03/2000	
Applicant's or agent's file reference 23201001/PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 99/08371	International filing date *(day/month/year)* 16/04/1999
Applicant CEDARS-SINAI HEALTH SYSTEM et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Mireille Claudepierre

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
23201001/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/08371	16/04/1999	16/04/1998
Applicant		
CEDARS-SINAI HEALTH SYSTEM et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readble form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/08371

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 45, 49, 50 and 52-56, as far as in vivo methods are concerned, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-57 (all partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-57 (all partially)

An isolated nucleic acid which encodes a human SH3D1A, analog, fragment, variant or mutant; said nucleic acid having at least 85% similarity with the nucleic acid sequence of SeqIdNo.1; said nucleic acid being DNA, RNA, cDNA, or genomic DNA; said nucleic acid encoding an amino acid sequence or a fragment of an amino acid sequence as set forth in SeqIdNo.2; said nucleic acid which is labeled with a detectable marker; an oligonucleotide of at least 15 nucleotides capable of specifically hybridizing with said nucleic acid; a molecule complementary to said nucleic acid; an antisense to said nucleic acid; a vector, vector system, and recombinant and purification techniques relating to said nucleic acid and its encoded polypeptide; a polypeptide comprising the amino acid sequence of a human SH3D1A; said polypeptide wherein the amino acid sequence is set forth in SeqIdNo.2 (Figure 5); a fusion protein comprising said polypeptide; an antibody to said polypeptide; a diagnostic method employing said nucleic acid, said polypeptide or said antibody; a method of suppressing cells unable to regulate themselves comprising the use of said polypeptide; a method for identifying a compound capable of suppressing cells unable to regulate themselves comprising said polypeptide; a pharmaceutical composition comprising said polypeptide or said nucleic acid; a transgenic non-human mammal comprising said nucleic acid.

2. Claims: 1-57 (all partially)

As for subject 1, but respectively relating to SeqIdNo.3 and SeqIdNo.4 through to SeqIdNo.38 (Figure 9).

3. Claims: 1-57 (all partially)

As for subject 1, but respectively relating to SeqIdNo.39 and SeqIdNo.40 through to SeqIdNo.70 (Figure 11).

4. Claims: 1-57 (all partially)

As for subject 1, but respectively relating to SeqIdNo.71 and SeqIdNo.72 through to SeqIdNo.75 (Figure 13).

5. Claims: 1-57 (all partially)

As for subject 1, but respectively relating to SeqIdNo.76 and SeqIdNo.77 through to SeqIdNo.104 (Figure 15).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/08371

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N15/11 C12N15/63 C12N15/62 C12N5/10
C12N1/21 C07K14/47 C07K16/18 A61K31/70 A61K38/17
A61K48/00 G01N33/50 G01N33/53 G01N33/68 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K G01N C12Q A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN H AND ANTONARAKIS S: "The SH3D1A gene maps to human chromosome 21q22.1-->q22.2." CYTOGENET. CELL GENET., vol. 78, 1997, pages 213-215, XP000857354 cited in the application the whole document	1-4,9-33
X	-& SPARKS A ET AL: "Cloning of ligand targets: systematic isolation of SH3 domain-containing proteins" NAT. BIOTECHNOL., vol. 14, no. 6, June 1996 (1996-06), pages 741-744, XP002124425 cited in the application SH3P17 in figures 3 and 4	1-4,9-33
X	-& DATABASE SWISSPROT [Online] Accession Number:Q15811, 1 November 1997 (1997-11-01) CHEN H ET AL: "Intersectin (SH3 -/--	1-4,9-33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 1999	07. 03. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lonnoy, O

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/08371

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	domain-containing protein SH3P17) / ITSN or SH3D1A / Human" XP002124426 100% identity in 519 aa overlap with SeqIdNo.2, abstract --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 1999	07. 03. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lonnoy, O

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 31625 A (CYTOGEN CORP ;UNIV NORTH CAROLINA (US)) 10 October 1996 (1996-10-10) SH3P17: SeqIdNo.37: 99.9% identity in 1389nt overlap with SeqIdNo.1 / SeqIdNo.38: 98.8% identity in 421aa overlap with SeqIdNo.2	1-4,9-33
X	-& DATABASE GENESEQ [Online] E.M.B.L. Databases Accession Number: W05395, 19 February 1998 (1998-02-19) FOWLKES D ET AL: "Human SH3P17 protein" XP002124457 98.8% identity in 421aa overlap with SeqIdNo.2 abstract	1-4,9-33
E	WO 99 55728 A (EGAN SEAN E ;HSC RES DEV LP (CA); SENGAR AMEET (CA); WANG WEI (CA)) 4 November 1999 (1999-11-04) SeqIdNo.1: 85.6% identity in 3174nt overlap with SeqIdNo.1	21,22
A	US 5 717 067 A (FAZIOLI FRANCESCA ET AL) 10 February 1998 (1998-02-10) Human Eps15 protein: 26.7% identity in 539aa overlap with SeqIdNo.2	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/08371

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9631625 A	10-10-1996	AU 711141 B	07-10-1999
		AU 5382196 A	23-10-1996
		CA 2217641 A	10-10-1996
		EP 0833941 A	08-04-1998
		JP 11509172 T	17-08-1999
		ZA 9602813 A	09-10-1996
WO 9955728 A	04-11-1999	NONE	
US 5717067 A	10-02-1998	US 5487979 A	30-01-1996
		US 5378809 A	03-01-1995
		US 5872219 A	16-02-1999
		AU 4838093 A	15-03-1994
		WO 9404571 A	03-03-1996
		US 5610018 A	11-03-1997

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

JACKSON, David A.
KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, New Jersey 07601
ETATS-UNIS D'AMERIQUE

RECEIVED
JUL 10 2000
KLAUBER & JACKSON

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 04.07.2000
Applicant's or agent's file reference 23201001/PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/08371	16/04/1999	16/04/1998

Applicant
CEDARS-SINAI HEALTH SYSTEM et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Christensen, J Tel.+49 89 2399-8052

Form PCT/IPEA/416 (July 1992)

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PATENT COOPERATION TREATY

REC'D 05 JUL 2000

WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
23201001/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/08371	16/04/1999	16/04/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant CEDARS-SINAI HEALTH SYSTEM et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/11/1999	04.07.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Roscoe, R Telephone No. +49 89 2399 2554

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/08371

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-59 as originally filed

Claims, No.:

1-57 as originally filed

Drawings, sheets:

1/30-30/30 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. (1-57)part.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-8, 15, 16, 19, 20, 37-57
	No:	Claims	1-4, 9-14, 17, 18, 21-36
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-57
Industrial applicability (IA)	Yes:	Claims	1-44, 46-48, 51, 57
	No:	Claims	45, 49, 50, 52-56

2. Citations and explanations

   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Citations

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

Note: since the present claims (insofar as they relate to the invention group being examined) appear to be entitled to priority from 16.4.98. Hence, D6 is not considered as relevant prior art

IV. **Lack of Unity**

The present application is considered non-unitary for the reasons set out on form PCT/ISA/210 in the Intl. Search Report. Since applicant has failed to pay additional search fees, the Search Report only relates to the first invention (matter relating to sequence ID Nos. 1 and 2). Hence, examination has to be restricted to this subject-matter.

V. **Reasoned statement on Novelty, Inventive Step and Industrial Applicability**

- **Novelty (Art.33(2) PCT)**

D1 discloses database sequence entries for parts of SH3D1A, provides and confirms a partial amino acid sequence and describes various primers which hybridize to the sequence. Hence, D1 anticipates claims 1-4, 14, 17, 18, 21, 22, 23.

D2 provides the first sequence of SH3P17 encoding nucleic acid. The nucleic acid has 97.3% identity in a 1942 bp overlap with Seq.ID No.1 of the present application. The nucleic acid comprises 4 SH3 domains. D2 anticipates claims1-4, 9-14, 17, 18, 21, 22, 23.

D3 discloses a protein sequence of SH3P17 which is 100% identical to 519aa of Seq. ID No.2. Hence, D3 anticipates claims 32 and 33.

D4 is a patent application by the authors of D2. D4 discloses a slightly different sequence for SH3P17. Seq.ID No.37 has 99.9% identity in 1389 nt overlap, with corresponding protein being 98.8% identical in 421aa overlap (this protein sequence is as in D5), compared to Seq.ID Nos 1 and 2 of the present application, respectively. D4 further discloses fusion proteins (see e.g. claim 80), vectors, recombinant cells (83-85 + p.66-), methods of producing protein (e.g. claim 88-), antibodies which bind the peptide (claim 99 + p.74-) and various methods for screening for modulators. D4 anticipates claims 1-4, 9-14, 17, 18, 21-36 .

Also claim 57 lacks novelty since any transgenic animal will have nucleic acid of claim 1. In animal DNA no longer "isolated" so this feature irrelevant.

- **Inventive Step (Art.33(3) PCT)**

Given that more than half of the SH3D1A gene had been isolated and sequenced prior to the present application (D1-D4) and that evidently (according to the applicant (p.57, l.23-) genomic DNA spanning this region was available. It is clearly trivial to complete the sequencing of the gene. The fact that the protein encoded by the gene was already known to have four SH3 domains (which are implicated in various cellular processes (see D4, p.6, "regarding SH3...")) provides the motivation to do so, as does the proposed involvement of the gene in the pathogenesis of Downs Syndrome (see e.g. D1). Hence, claims to SH3D1A nucleic acids or protein are not considered inventive, the same applying to trivial routine items relating thereto such as vectors containing the DNA, host cells expressing the DNA etc. (i.e. claims 1-36). Similarly, looking for mutations by standard techniques in a non-inventive gene cannot be considered inventive per se (i.e. claims 37-39, 46-47). Claims 40-44 relate to the detection of megakaryocytic abnormality, hematopoetic disorders, myeloproliferative disorders, platelet disorder, leukemia or neural disorder. Claims 49-50 monitoring progress of treatment of disorders listed in claim 40. Claims 52-56 relate to method of treating disorders listed in claim 40. Since these disorders are very broadly defined and it is known that proteins having SH3 domains are implicated in cell growth and oncogenesis (for example), claims founded on this basis are not considered inventive. Claim 45 is a method of suppressing cells using SH3D1A

(and claim 48 is for a finding a compound which inhibits SH3D1A and thus suppresses cells !? illogical, since claims based on contradictory theory of proteins function !). The basis for these claims is presumably the know suppressor function of SH3 domains. Since the presence of these in SH3D1A was already known and no further evidence for this function forms part of the application, these claims are not considered inventive. Claim 51 relates to a pharmaceutical composition. Formulating a pharmaceutical composition from a known protein is not inventive per se unless a unexpected pharmaceutical effect can be demonstrated. Hence, the present claims are not considered inventive. It is further noted that since SH3D1A is not considered inventive, no unifying concept spans the sets of claims mentioned above. (at present, this unity objection shall not be persued for practical reasons).

- **Industrial Applicability (Art.33(4) PCT)**

For the assessment of the present claims 45, 49, 50, 52-56 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 45, 49, 50, 52-56 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

VI. Certain documents

In accordance with Rule 70.10, PCT, applicants attention is drawn to the following document(s):

WO-A-99/55728 (Publication date, 04.11.99; Priority dates, 27.04.98, 05.02.99;

Filing date, 27.04.99)

VIII. **Certain observations**

- **Clarity (Art.6 PCT)**

It seems that the term SH3D1a embraces a number of different proteins, a number of which are known. Hence, the term needs to be defined exactly in the present application by sequence data which defines the exact splice variant in question.

Claim 1 - "analogs,...,mutants" all undefined in both length and nature. Also claim to a result to be achieved - result i.e. sequence not in claim.

Claim 2 - no length nucleic acid specified

Claims 8-13 - double use of abouts in context of ranges unallowable.

Claims 9 and 13 identical

Claim 14 - "an amino acid..." should be replaced by "the amino acid...." or size undefined.

Claim 17 - hybridization conditions ?, hybridization to degenerate sequence, (non-unitary)

Claims 21 and 22 - how long ?, 22 also hyb. cond. ?

Claim 25 should refer to claim 24

Claim 32 - define by seq.

Claim 36 - should refer to 35(presumably)
Claims 38 and 39 - dependencies obviously wrong

Claim 51 - reference to polypeptide of claim 1 but claim 1 relates to nucleic acid

Fig. sheet 3/30 is blank. Since it appears that it was not filed, addition of the figure at this stage cannot be allowed since it would constitute unallowable added matter.

- **Support in Description (Art.6, PCT) + Sufficiency of disclosure (Art.5, PCT)**

Claims relating to the medical relevance of SH3D1A lack any technical basis in the application documents, insofar as they extend beyond the observation mentioned in the experimental details section introductory paragraph (no corresponding experiment is evident in the following section) that SH3D1A expression is elevated in lymphoblastoid cells. Further, elevated expression may be the result, not the cause, of the condition - thus not providing a technical basis for the broad medically related claims in the application.

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

by fax and post

PCT

WRITTEN OPINION

(PCT Rule 66)

To:
JACKSON, David A.
KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, New Jersey 07601
ETATS-UNIS D'AMERIQUE

RECEIVED
APR 20 2000
KLAUBER & JACKSON

Fax 201 343 1684

Date of mailing *(day/month/year)*	11.04.2000
Applicant's or agent's file reference: 23201001/PCT	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/08371	16/04/1999	16/04/1998

International Patent Classification (IPC) or both national classification and IPC
C12N15/12

Applicant
CEDARS-SINAI HEALTH SYSTEM et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 16/08/2000.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Roscoe, R

Formalities officer (incl. extension of time limits)
Vullo, C
Telephone No. +49 89 2399 8061

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-59 as originally filed

Claims, No.:

1-57 as originally filed

Drawings, sheets:

1/30-30/30 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons

and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

see separate sheet

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☐ all parts.

☒ the parts relating to claims Nos. (1-57)part.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4, 9-14, 17, 18, 21-36
Inventive step (IS)	Claims	1-57
Industrial applicability (IA)	Claims	45, 49, 50, 52-56

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Citations

The documents mentioned in the present written opinion / International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

Note: since the present claims (insofar as they relate to the invention group being examined) appear to be entitled to priority from 16.4.98. Hence, D6 is not considered as relevant prior art

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Also claim 57 lacks novelty since any transgenic animal will have nucleic acid of claim 1. In animal DNA no longer "isolated" so this feature irrelevant.

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Claims 45, 49, 50, 52-56 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

VI. **Certain documents**

In accordance with Rule 70.10, PCT, applicants attention is drawn to the following document(s):

WO-A-99/55728 (Publication date, 04.11.99; Priority dates, 27.04.98, 05.02.99;

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Fig. sheet 3/30 is blank. Since it appears that it was not filed, addition of the figure at this stage cannot be allowed since it would constitute unallowable added matter.

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Claims relating to the medical relevance of SH3D1A lack any technical basis in the application documents, insofar as they extend beyond the observation mentioned in the experimental details section introductory paragraph (no corresponding experiment is evident in the following section) that SH3D1A expression is elevated in lymphoblastoid cells. Further, elevated expression may be the result, not the cause, of the condition - thus not providing a technical basis for the broad medically related claims in the application.

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Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.